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Syntelencephaly in an Infant of a Diabetic Mother

Nathaniel H. Robin, Lara M. Ko, Shauna Heeger, Kevin L. Muise, Nancy Judge, and Barbara A. Bangert

Center for Human Genetics, Departments of Genetics (N.H.R., L.M.K., S.H.), Pediatrics (N.H.R.), Department of OB-Gyn (K.L.M., N.J.), Department of Radiology (B.A.B.), Case Western Reserve University School of Medicine and University Hospitals of Cleveland, Cleveland, Ohio

Here we report on an infant of a diabetic mother (IDM) with midline interhemispheric "fusion" (MIF), or syntelencephaly. This is a rare anomaly characterized by segmental failure of cleavage of the cerebral hemispheres and other brain structures in the posterior frontal and parietal regions, with a normal interhemispheric fissure anterior and posterior to the "fused" region. While there is obvious overlap with holoprosencephaly (HPE), this condition differs from HPE in that the midline "fusion" in MIF is complete but segmental, while the structural brain anomalies seen in the HPE spectrum progress smoothly in severity in a posterior to anterior "fusion." However, while it is apparent that there are key distinctions between MIF and HPE, in all likelihood they arise from a similar pathogenetic mechanism. We therefore suggest that MIF is a distinct variant of the HPE spectrum of midline brain anomalies. Given the known increased incidence of HPE in IDMs, MIF is likely a maternal diabetes-associated malformation. © 1996 Wiley-Liss, Inc.

KEY WORDS: middle interhemispheric fusion, syntelencephaly, holoprosencephaly, midline brain malformation, infant of a diabetic mother

INTRODUCTION

Middle interhemispheric "fusion" (MIF), or syntelencephaly, is characterized by segmental "fusion" of the cerebral hemispheres and other midline brain structures in the posterior frontal and parietal regions, but with a normal interhemispheric fissure present anterior and posterior to the fused region [Oba and Barkovich, 1995]. It is a rare anomaly, with few cases described to date [Barkovich and Quint, 1993]. In these few reports, it was debated whether MIF represents a distinct anomaly of midline development or is a variant of holoprosencephaly (HPE). In both, the primary finding is "fusion" of midline brain structures. However, the complete segmental "fusion" of the cerebral hemispheres and thalami in MIF differentiate it from the type of midline fusion seen in HPE. There, severity increases with a smooth posterior to anterior progression of the degree of "fusion" [Leech and Shuman, 1986; Cohen and Sulik, 1992].

Here we report on an infant of a diabetic mother with MIF, and compare this patient to those reported previously. In addition, we review the possible pathogenesis of MIF, and its relationship to the HPE spectrum of anomalies.

CLINICAL REPORT

The child was born to a 17-year-old woman and a non-consanguineous 21-year-old man. Family histories were obtained and showed no birth defects, unexplained neonatal deaths, or suspected genetic disorders. The woman's previous pregnancy ended in a first trimester spontaneous abortion. She has been an insulin-dependent diabetic since the age of 14 years and was known to be in poor glycemic control during the early part of this pregnancy. Alcohol, cigarette, and illicit drug use were denied. Ultrasound examination at 17 weeks gestation showed a singleton fetus with an absent corpus callosum and abnormally configured cerebral ventricles, with evidence of midline "fusion." This prompted the diagnosis of lobar holoprosencephaly. There were no other abnormal craniofacial findings, and no other structural anomalies were identified. Amniocentesis was performed and a 46,XX karyotype at the 475 band level was found.

After counseling, the patient chose to continue her pregnancy. She delivered by spontaneous vaginal delivery at term, with no complications. Because of the antenatal diagnosis of lobar HPE, the newborn infant was taken to the neonatal intensive care unit for evaluation. Physical examination at that time included a birthweight of 3,705 g (85th centile), a length of 50 cm (50–75th centile), and a head circumference of (OFC) 34 cm (50th centile). Craniofacial examination showed

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Address reprint requests to Dr. Nathaniel H. Robin, Center for Human Genetics, Lakeside 1500, 11100 Euclid Ave, Cleveland, OH 44106.

a symmetric, normally shaped cranium, with an anterior fontanelle of 2 × 2 cm, and a pinpoint posterior fontanelle. The eyes were normally formed and placed, with an interpupillary distance of 4.2 cm (60th centile). The ears were also normally formed and placed, as was the nose and mouth, including a normal palate. However, there was no anterior maxillary frenulum of the upper lip (Fig. 1). The remainder of the physical findings, including the chest, heart, abdomen, genitalia, and limbs were normal. Neurologically, the infant was alert and interactive, with no obvious deficit. Neurologically, the baby was vigorous, moved all four limbs equally, with normal tone. In addition, patellar tendon and other neonatal reflexes were normal.

The infant underwent numerous imaging studies, including a normal echocardiogram and renal ultrasound. However, ultrasound examination of the head showed an absent corpus callosum with dilated periventricular space. Magnetic resonance imaging (MRI) was performed to further delineate the abnormal brain anatomy (Fig. 2a–d).

T1 weighted sagittal, coronal, and axial images of the head as well as multiecho axial images of the head were obtained. These showed a partially absent corpus callosum. While the genu and anterior part of the body was visualized, very little of the main portion of the body of the corpus callosum was apparent, and only a rudimentary splenium was seen. In addition, at the point where the corpus callosum is hypoplastic, there was almost complete absence of the falx with a segmental lack of separation of the hemispheres in the parietal region. There was thalamic and corpus striatum "fusion," and the frontal horns were slightly hypoplastic. In the occipital and frontal regions, a normal interhemispheric fissure and normal falx were apparent. Of note, there is a suggestion of a partial septum pellucidum. No definite heterotopias are identified, although gray matter did fold into the region of the absent corpus callosum body in a somewhat disorganized manner. A normal myelination pattern was evident.

Presently, at age 2 months, the child is developmentally appropriate, alert and interactive, and feeding well.

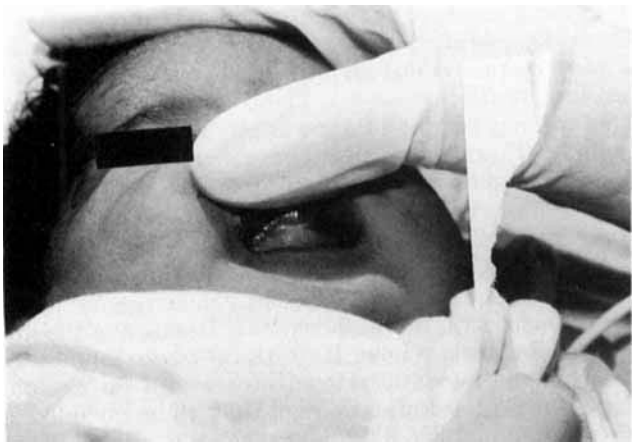

Fig. 1. Patient in the neonatal period. Note the absent anterior maxillary frenulum.

DISCUSSION

This infant shares many findings with the few previously reported patients with MIF (Table I). Namely, these individuals had normal facial appearance, with no external physical manifestations suggestive of HPE, such as hypotelorism or cleft lip and palate, and had only developmental delay in common. However, these previous cases were not evaluated by a clinical geneticist, so it is possible that subtle signs may have been overlooked. In our patient, the only external manifestation was an absent frenulum, which has been shown to be a subtle sign in some patients with HPE [Martin et al., 1994].

It is interesting to note that our patient was an IDM. Maternal insulin-dependent diabetes, especially if poorly controlled, is a well-established cause of malformations in the developing human fetus [Becerra et al., 1990]. Although there is a 2–4-fold elevated risk for all birth defects in IDM [Eriksson, 1995], the most common malformations are sacral agenesis, complex cardiac defects, anencephaly, and HPE [Kučera, 1971]. These are malformations that arise during blastogenesis, at the end of week 4 of development [Opitz, 1993]. While the exact mechanisms are not yet defined, it is clear that elevated glucose levels in maternal diabetes are not the sole cause of malformations [Eriksson, 1995]. Rather, animal studies have suggested that free oxygen radicals, possibly generated by embryonic mitochondria exposed to elevated glucose levels (and possibly other compounds) [Eriksson and Borg, 1991, 1993]. Such free radicals may then alter prostaglandin synthesis, which would have a deleterious effect on the developing embryo [Eriksson, 1995]. This theory is supported by the observed benefit to embryos in a diabetic environment of arachadonic acid [Goldman et al., 1985; Pinter et al., 1986] and *myo*-inositol supplementation [Hashimoto et al., 1990; Baker et al., 1990].

Maternal insulin dependent diabetes is thought to increases the risk for HPE to as high as 1% [Barr et al., 1983]. While the exact reason for this effect is unknown, in general it is thought that teratogens, or genetic abnormalities, cause HPE by interfering with the inductive influence of the prechordal mesenchyme on the neural plate during the period of gastrulation, or by interfering with the neural plate itself at a slightly later time [Leech and Shuman, 1986; Cohen and Sulik, 1992]. The prechordal mesenchyme is established just prior the formation of the prosencephalic vesicle, at day 35, in the area posterior to the newly formed optic chiasm [Leech and Shuman, 1986]. These cells have an effect on the neural plate cells, inducing the formation of the forebrain and other midline brain structures. In addition, the prechordal mesenchyme has an important role in the developing craniofacial region as well. This is evident by the spectrum of facial anomalies that usually parallel in severity the brain anomalies in HPE [DeMyer et al., 1963]. It is thought that this phenotypic spectrum of HPE may be related to slight differences in the timing, duration, or intensity of the insult, genetic or teratogenic, to the prechordal mesenchyme or neural plate [Cohen and Sulik, 1992].

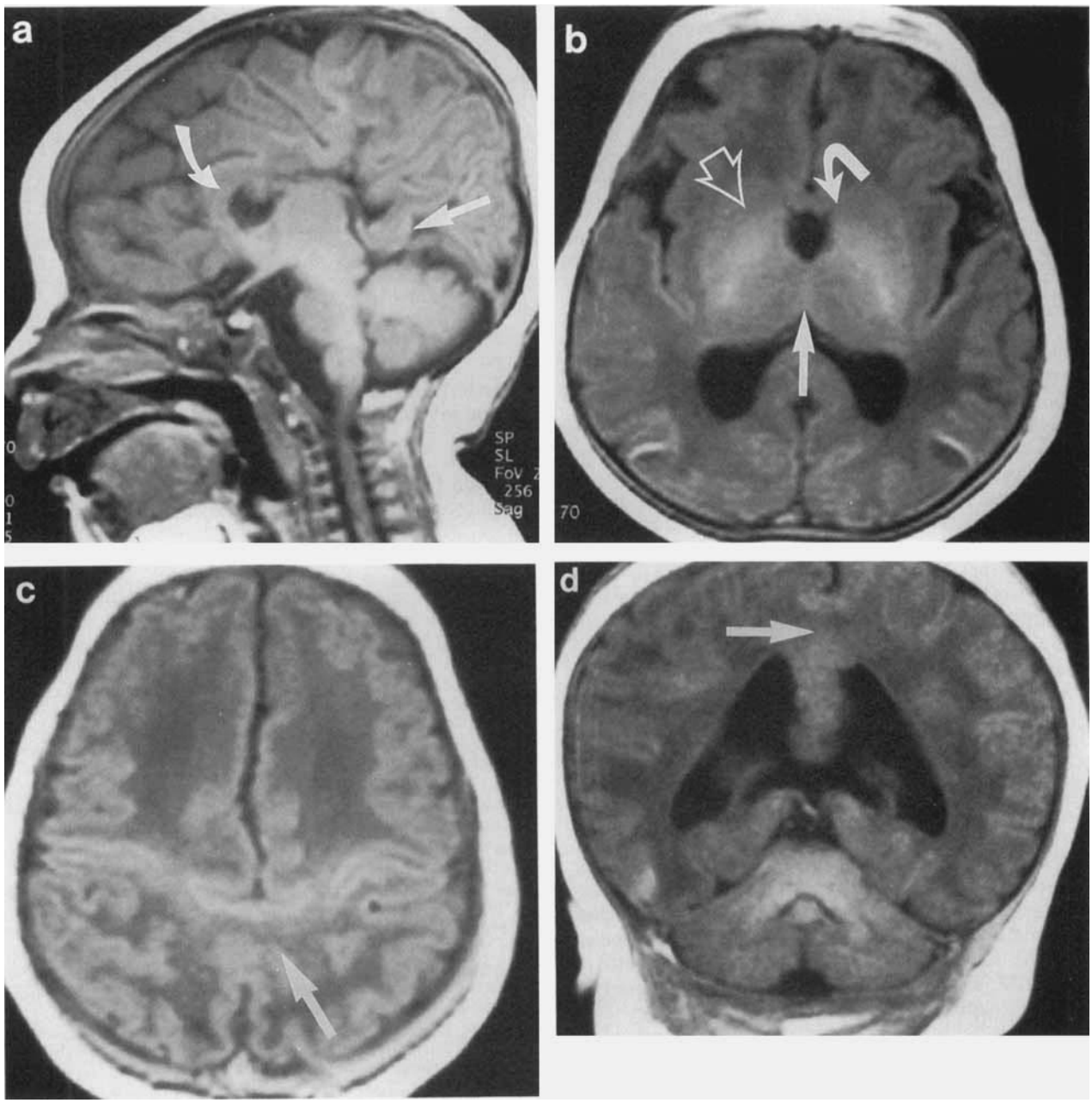

Fig. 2. **a**: T1 weighted sagittal MRI images demonstrating the genu of the corpus callosum (curved arrow) as well as a splenium-like structure posteriorly (straight arrow). **b**: T1 weighted axial image demonstrating hypoplastic frontal horns (curved arrow), and striatal (open arrow) as well as thalamic (straight arrow) "fusion". **c**: T1 weighted axial image demonstrating partial "fusion" of the hemispheres near the parietal convexity (arrow). **d**: T1 weighted coronal image also demonstrates the midline "fusion" in the parietal region (arrow).

What is interesting and seemingly distinct about MIF is the segmental nature of the anomaly. The normal development of the midline brain structures proceeds in an anterior to posterior direction [Leech and Shuman, 1986]. In HPE, while the degree of "fusion" is variable, it can be related to this normal developmental progression. In the most severe form of HPE, alobar HPE, there is a single cerebral hemisphere and a sickle-shaped holo-ventricle, and no evidence of a midline. This is often associated with severe craniofacial abnormalities, such as cyclopia (single or partially divided eye with a proboscis above), ethmocephaly (hypotelorism with a proboscis), or cebocephaly (hypotelorism with a single nostril). In the intermediate form, semi-lobar HPE, there is only posterior separation of the cerebral ventricles and hemisphere, with the

TABLE I. Comparison of Findings on MRI in Cases With Midline Interhemispheric Fusion

		Barkovic and Quint [1993]		
	This report	Patient 1	Patient 2	Patient 3
Age	Newborn	5 months	11 months	22 months
Reason for imaging	Prenatal diagnosis HPE	Developmental delay	Developmental delay	Developmental delay
Thalamic fusion	Partial	Present	Mild	Absent
Septum pellucidum	Rudimentary	Absent	Absent	Absent
Corpus callosum	Genu, anterior body present, remainder hypoplastic	Absent	Absent	Absent body
Cortical dysplasia	None	Bilateral diffuse	Not conclusive	Bilateral frontal
Dorsal cyst	Absent	Present	Absent	Absent

anterior part of the brain fused. These children often are hypoteloric, with a flat midface and nose, and a midline cleft lip and palate. In the mildest form, lobar HPE, affected children may be hypoteloric, or have only mild facial malformations [Cohen, 1989a,b; Muenke, 1994]. In these patients there is complete separation of the cerebral hemispheres and ventricles, although other midline structures may be fused, such as the thalami, or hypoplastic, such as the corpus callosum [Demeyer et al., 1963; Cohen and Sulik, 1992]. It is interesting to note that these brain "anomalies" may represent atavisms, as they are normal in some lower mammals. Absence of the corpus callosum is a normal finding in marsupials and monotremes (egg-laying animals), and "fused" thalami is normal in rabbits [Walker, 1964].

The smooth progression of severity in HPE contrasts with that seen in the reported cases of MIF. Here, the "fusion" is segmentally complete. In the posterior frontal and parietal regions, there is "fusion" of the cerebral hemispheres and the thalami, and focal hypoplasia of the corpus callosum. In the regions anterior and posterior to this segment, there is apparently normal separation of the cerebral hemispheres and other brain structures. In addition, there is evidence for presence of the septum pellucidum, a structure absent in cases of HPE [Barkovich, 1995]. So, while this anomaly of midline brain "fusion" shares some findings with HPE, there is evidence indicating that it may indeed be a separate entity. Perhaps complete ablation of a specific population of cells in the prechordal mesenchyme or neural plate that are destined to locate in the middle interhemispheric fissure and other midline brain structures is responsible. This would account for the lack of significant facial anomalies seen in these patients, as this region would be posterior, and not be expected to participate in induction of craniofacial development. It may be that these cells are especially susceptible to the teratogenic influences of the maternal diabetic state. Perhaps this anomaly is relatively specific to IDM. The prenatal history was not addressed in the previous report of this condition. Therefore, while it is apparent that there are key distinctions between MIF and HPE, in all likelihood they arise from a similar pathogenetic mechanism. So, while MIF does not fit into one of the defined categories of HPE, we would suggest it be classified as a separate variant of HPE that may possibly be specific to IDM.

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NOTE ADDED IN PROOF

At age 11 months, the child is delayed in her development, and has a single central incisor.

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